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Prior loss of body mass index, low body mass index, and central obesity independently contribute to higher rates of fractures in elderly women and men

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ABSTRACT

We aimed to comprehensively evaluate the association of body composition with fracture risk using longitudinal data from a Swedish cohort of 44,366 women and men (mean age of 70 years) and a subcohort of 5022 women. We estimated hazard ratios (HRs) of fracture for baseline body mass index (BMI), BMI change during the prior 12 and 18 years, baseline waist-to-height ratio, total and regional distribution of fat and lean mass, with and without areal bone mineral density (BMD) adjustment. During follow-up (median 8.7 years), 7290 individuals sustained a fracture, including 4279 fragility fractures, of which 1813 were hip fractures. Higher baseline BMI and prior gain in BMI were inversely associated with all types of fracture. Lower fracture rate with higher baseline BMI was seen within every category of prior BMI change, whereas higher prior BMI gain conferred a lower rate of fracture within those with normal baseline BMI. Each standard deviation (SD) higher baseline waist-to-height ratio, after adjustment for BMI, was associated with higher rates of hip fracture in both women and men (HR 1.12; 95% CI, 1.05–1.19). In the subcohort (median follow-up 10 years), higher baseline fat mass index (FMI) and appendicular lean mass index (LMI) showed fracture-protective effects. After BMD adjustment, higher baseline BMI, total LMI, FMI, and higher prior BMI gain were associated with higher fracture rate. Baseline fat distribution also was associated with fracture rate; a 1-SD higher android to gynoid fat mass ratio in prior BMI gainers was associated with BMD-adjusted HRs of 1.16 (95% CI, 1.05–1.28) for any fracture and 1.48 (95% CI, 1.16–1.89) for hip fracture. This pattern was not observed among prior BMI losers. These findings indicate that for optimal fracture prevention, low baseline BMI, prior BMI loss and high baseline central obesity should be avoided in both women and men. © 2021 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: GENERAL POPULATION STUDIES; FRACTURE RISK ASSESSMENT; DXA; BODY MASS INDEX; BODY COMPOSITION

Introduction

Body composition shifts dramatically with adult aging: skeletal muscle mass declines on average 40% from young adulthood to age 80 years,[1] while body fat increases by over 50%.[2] Lifestyle changes have also driven obesity prevalence to epidemic proportions in recent decades, both in industrialized and developing countries.[3,4] Such changes could cause sarcopenic obesity and impaired physical performance, resulting in higher risk of falling.[5] In addition, central obesity has been found related to inferior bone quality.[6,7] The risk of hip fracture, the most devastating fragility fracture, is 44 times higher in Swedish women aged 85 years than in those aged 55 years.[8,9] Yet, the decrease in bone mineral density (BMD) during these three decades of aging only explains one-tenth of the variance of the higher fracture incidence at old age.[8,9] Although osteoporosis is a strong risk factor for fragility fractures, less than one in three hip fractures is attributable to osteoporosis,[10] and for other types of fragility fractures, the proportion is even lower.[10] The importance of changes in body composition with increasing age for the risk of different types of fracture is at present unclear.

Although it is known that high body mass index (BMI) remains a protective factor for most sites of fragility fracture,[11,12] there has been surprisingly little investigation of the changes in BMI

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with increasing age and detailed analysis of body composition in relation to risk of fractures. Only the Tromsø study (n = 10,977) has prospectively investigated change of BMI in relation to fracture risk,[13] and no study has evaluated the combined impact of baseline BMI and prior change in BMI. Findings from prospective studies on the association between abdominal obesity as measured by waist-to-hip ratio and the risk of hip fracture are conflicting.[14] Furthermore, only one cohort[15] has evaluated fracture risk with lean and fat mass by whole-body dual-energy x-ray absorptiometry (DXA) scans in addition to BMD. Fracture risk in relation to estimated total lean mass and fat mass (based on DXA scans at the hip and spine, body weight, and sex) and their changes has, however, been evaluated.[16,17]

By use of a large longitudinal population-based cohort we investigated the independent contribution of baseline BMI, prior BMI change, and waist-to-height ratio on the rate of any, fragility, and hip fractures in women and men. In addition, we used a subcohort of women with more detailed body composition information to evaluate the contribution of total and regional body composition measures of fat and lean mass to fracture rate, with and without taking BMD into consideration.

Subjects and Methods

Study population

The Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM) are two large population-based prospective cohorts, part of the Swedish Infrastructure for Medical Population-based Life-course and Environmental Research (SIMPLER; https://www.simpler4health.se/). The SMC was established in 1987–1990 when all women (n = 90,303) born in 1914–1948 and residing in two Swedish counties (Västmanland and Uppsala) were invited to participate in the study through a mailed questionnaire covering questions on body weight, height, diet, and lifestyle.[18] In total 66,651 women returned a completed questionnaire (response rate 74%). In 1997 and 2008–2009, extended follow-up questionnaires were sent out to the women, 39,984 (70%) and 30,621 (63%), respectively, responded. COSM was established in late 1997 when all male residents (n = 100,303) of two counties (Örebro and Västmanland) born between 1918 and 1952 were invited to participate; 48,850 responded. In 2008–2009, a second questionnaire was sent to all COSM members and 29,503 (78%) responded.[18] When compared to the Official Statistics of Sweden, the cohorts well represented the Swedish population in 1997 in terms of age distribution, educational level, prevalence of overweight and obesity, and smoking status.[18,19]

During November 2003 through September 2009, a random sample of SMC women who had replied to the questionnaires and were living in Uppsala city or the surrounding area were invited to undergo DXA, provide fasting blood and urine samples and fat biopsies, and have height and weight measured. A total of 5022 women took part (participation rate 65%) and comprised our clinical subcohort. Before the clinical examination, a third questionnaire requesting updated lifestyle information was completed by the participants.[20]

The present analysis focuses on two populations: the "full cohort" of all respondents to the 2008–2009 questionnaires and participants in the subcohort. Women and men with a diagnosis of any type of cancer before 2009 (16%), missing information on anthropometric information (4%), or a BMI below 18.5 kg/m^2 (1%) were excluded for the present study, leaving a final cohort of 44,366 women and men. We used the subcohort of women for more detailed analyses of different body composition measures. The baseline was April 14, 2009 (after receipt of the last questionnaire) for the full cohort and the date of the clinical examination in 2003–2009 for the subcohort.

A time plot of data collection for the full cohort, the subcohort, and their follow-ups is shown in Figure 1. The study is approved by the regional ethics committee and informed consent was obtained from all participants.

BMI, prior BMI change, and body composition measures

Full cohort

BMI was calculated as kg/m^2. We further categorized BMI,[21] into normal (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), and obese (≥30 kg/m^2). In the full cohort, prior change in BMI was estimated from self-reported change between 1997 and 2008–2009, a mean interval of 12 years.

Participants with prior BMI loss greater than 0.5 kg/m^2 were classified as "prior BMI losers", those with prior BMI loss lower than 0.5 kg/m^2 up to an increase of 2 kg/m^2 were deemed "prior BMI maintainers", and those with a prior BMI increase of more than 2 kg/m^2 as "prior BMI gainers". Our intention was to select BMI change categories that on average reflect meaningful changes while also containing a sufficient number of exposed participants in each category. We also calculated the baseline waist-to-height ratio (WHtR) by use of self-reported waist circumference (cm) divided by height (cm) as a measure of central obesity because WHtR has been shown as a more sensitive health risk indicator than waist circumference or waist to hip circumference ratio.[22,23] WHtR was also classified into three categories: <0.5, 0.5 to <0.6, and ≥0.6.[24,25]

Subcohort

In the subcohort, prior change in BMI was estimated from 1987-1990 (date of the first questionnaire in women) to baseline, a median interval of 18 years with a range of 14 to 22 years; baseline weight and height were measured with a scale and a stadiometer, respectively. Prior BMI change category in the subcohort was classified as in the full cohort, using the same cutoffs. We have more detailed information of body composition in the subcohort. At baseline of the subcohort, measurement of total body and regional lean, fat, and bone mass from whole-body scans by DXA (Lunar Prodigy, Lunar Corp, Madison, WI, USA) was conducted. With use of the same equipment, areal BMD (g/cm^2) at the total hip (bilateral, mean value used), femoral neck (also mean value of dual hip scans), lumbar spine (L_1–L_4), and total body was measured as described.[20,26] In addition to BMI, total lean mass index (LMI), appendicular LMI, and total fat mass index (FMI) were calculated by dividing total body lean mass (LM), appendicular LM, and total body fat mass (FM) by height squared, respectively. Android (A) FM and gynoid (G) FM were determined using the software provided by the manufacturer with the android region representing the abdomen and the gynoid region representing gluteofemoral area.[27] The android to gynoid FM ratio (A/G FM) was calculated as the measure of central obesity in the subcohort.

The precision errors on triple DXA scans in 15 participants, including repositioning, were 0.8% to 1.5% depending on type of measurement (lean mass, fat mass, or BMD) and site. The long-term coefficient of variation was less than 1% for a spine phantom. The validity of fat mass derived by Lunar Prodigy has

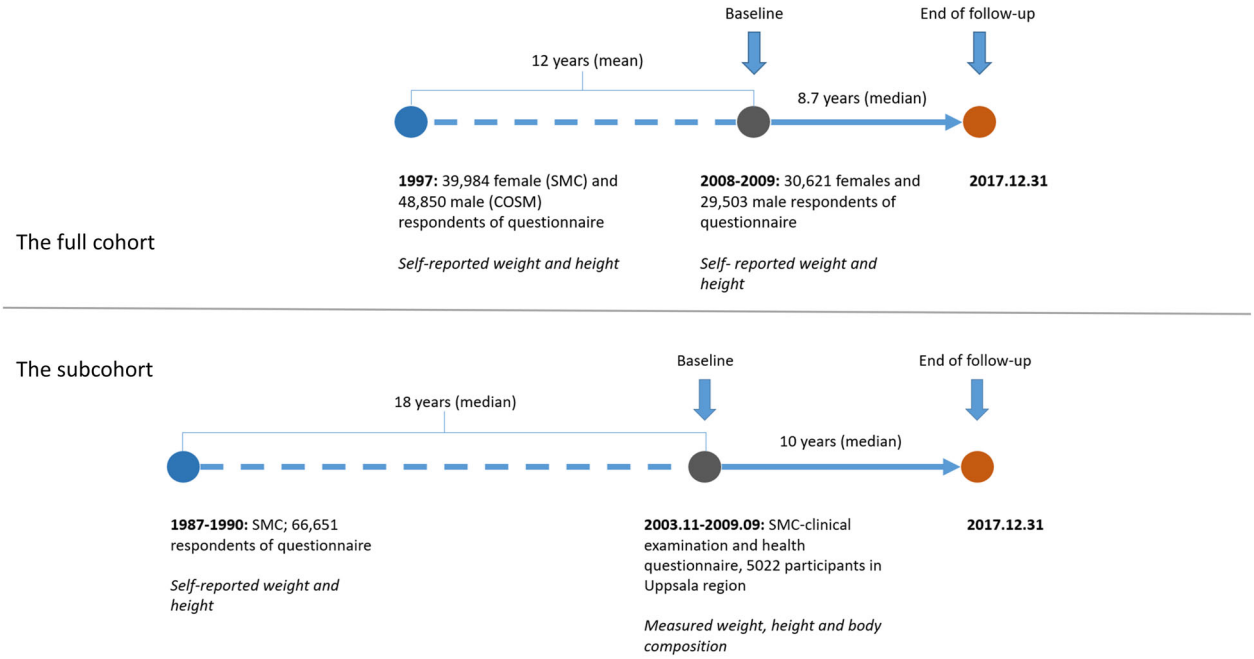

Fig. 1. Timeline of data collection and follow-up of the full cohort (including both the COSM and the SMC, and the SMC-clinical). Abbreviations: COSM, cohort of Swedish men; SMC, Swedish mammography cohort; SMC-clinical, clinical subcohort of SMC.

been evaluated against the four-compartment model, the tool that is currently considered the gold standard method of body composition appraisal, resulting in 1.7% to 2.0% higher fat mass estimates with this narrow fan-beam DXA equipment.[28]

Definition of *T*-score osteoporosis and low lean mass

T-score osteoporosis was defined as an areal BMD *T*-score < −2.5 at the total hip, femoral neck, or lumbar spine[29] and appendicular LMI <5.45 kg/m^2 was considered to be low lean mass, one definition of sarcopenia.[30] Participants in the subcohort were classified into four groups based on cross-classification of low lean mass and *T*-score osteoporosis.

Fracture ascertainment

We collected fracture events by linkage with the Swedish national inpatient and outpatient (active since 2001) registries using the Swedish personal registration number provided to all Swedish citizens. A fracture in this study was defined as a hospital admission or an outpatient visit with an International Classification of Diseases 10th edition (ICD-10) fracture codes S12–S92. Fragility fracture was classified as those occurring at the lumbar spine or pelvis (S32), proximal humerus (S42.2), distal forearm (S52.5), or hip (S72.0–S72.2). Hip fracture was considered separately as an additional outcome. Incident fractures were identified by the use of a previously validated and accurate algorithm[31]; only the first fracture event after baseline was used in the main analysis. We retained information about previous fractures for the purpose of sensitivity analysis. Pathological fractures due to cancer were not included but fractures apparently caused by high-impact trauma were retained in the analysis because the risk for both low-trauma and high-trauma fractures are similarly related to BMD.[32,33]

Comorbidity

Charlson's weighted comorbidity index (CCI)[34] was calculated by collating diagnosis codes from the national inpatient registry from 1964 until baseline. Diabetes was additionally considered as a separate variable, defined as self-reported diabetes with or without treatment with insulin or oral hypoglycemic agents and/or as fasting plasma glucose ≥7.0 mmol/L (in the subcohort only).

Statistical analyses

Descriptive statistics for baseline characteristics in the full cohort and the subcohort are presented across groups of prior BMI change. For each individual, we calculated time at risk from baseline until the date of the fracture, death, or the end of the study period (December 31, 2017), whichever occurred first. Age-adjusted and multivariable-adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for rate of any, fragility, and hip fractures by each exposure were estimated by Cox proportional-hazards regression. The anthropometric and body composition variables were mean centered and scaled to 1 standard deviation (SD). The proportional-hazards assumption of the Cox regressions was assessed using Schoenfeld residuals plots. No deviation from proportionality was detected.

For the full cohort, combinations of the categories of prior BMI change and baseline BMI as well as categories of prior BMI change and baseline WHtR were used to jointly classify study participants into nine strata for each of the combinations (BMI change*BMI and BMI change*WHtR). Participants with baseline overweight or mid-category of WHtR combined with prior gain in BMI were used as the reference category in these analyses because this group contained the largest number of individuals. The impact of prior BMI change, baseline BMI, and WHtR as

continuous variables on the rate of fracture was evaluated within each category of the anthropometric exposures, and tests for multiplicative interaction of these estimates across the categories were conducted. We also evaluated multiplicative interactions between sex and the anthropometric measures. In the subcohort, we evaluated the associations of baseline A/G FM and fracture rate within prior BMI losers, maintainers, and gainers, and also fracture rate in combination categories of *T*-score osteoporosis and low lean mass.

Directed acyclic graph (DAG) was used to illustrate the underlying causal assumptions for our research questions and to identify factors to include as covariates to limit bias due to confounding (Supplemental Fig. S1). Covariates included were as follows: age, height, weighted CCI, and daily alcohol intake (all continuous), diabetes mellitus (yes/no), current smoking (yes/no), and leisure time exercise level (level 1 to 5) at baseline. However, we found that adjustment for the covariates only marginally changed the age-adjusted estimates and thus the more parsimonious age-adjusted model was used as the main model. When evaluating the direct effect of baseline central obesity on fracture rate, as WHtR and A/G FM, we additionally adjusted for baseline BMI. We further used a baseline age- and total hip BMD-adjusted model to evaluate BMD-independent associations in the subcohort. Single imputation was used for missing covariates in the subcohort (the mean value for continuous covariates and the most frequent level for categorical covariates) because this approach seems to suffice when missing values of all covariates are rare (<7% in the subcohort).[35] For the analysis of the full cohort, missing data were imputed (20 imputations) using Stata's ''mi'' package (multiple imputations using chained equations) (Stata Corporation, Inc., College Station, TX, USA). The proportions of missing data in the full cohort were 13% for exercise, 17% for smoking and 11% for alcohol intake. For all other covariates, the percent missing was less than 2%. All analyses were carried out in R (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/) and Stata MP (version 15) for Linux.

Sensitivity analyses in the subcohort

Because the weight and height data collected in 1987–1990, 1997, and 2008-2009 were self-reported, we evaluated the impact of bias between self-reported and measured data by comparing self-reported data in 2008–2009 with measured baseline data in the subcohort. Self-reported body weight was 0.9 kg lower on average than that measured. Among those with normal weight, overweight, and obesity, the body weight was underreported by a mean of 0.33, 1.86, and 3.22 kg, respectively. Thus, in a sensitivity analysis of the subcohort we added these differences to the self-reported weight in 1987–1990 by BMI category and evaluated the impact of this modulation on the fracture rate by 1987–1990 BMI and BMI change from 1987–1990 to baseline. Comparisons of self-reported height, waist circumference, and longitudinal changes of weight and height to the measured ones are detailed in the Supporting Information.

In further sensitivity analyses, we adjusted for LMI when fat mass measures were used as exposures in the subcohort and for FMI when lean mass measures were used as exposures, thus taking into account the positive correlation between fat mass and lean mass. The estimates of anthropometric and body composition were further adjusted for previous fractures (yes/no) or fall risk increasing drugs (FRIDs) use (yes/no) in addition to age and variables included in the multivariable model. FRIDs were defined as any use of the Anatomical Therapeutic Chemical (ATC) codes: N02A, N03A, N04A-B, N05A-C, N06A, C01A, C01BA, C01D, C02, C03, C07-C09, and G04CA.

Results

The characteristics of participants at baseline by category of prior BMI change are shown in Table 1. The average age at baseline in both the full cohort and the subcohort was approximately 70 years. The women in the full cohort and subcohort were postmenopausal, with at least 61 years of age at baseline for the present analysis. Prior BMI gainers had the highest baseline BMI, appendicular and total LMI, FMI, A/G FM and total hip BMD, whereas BMI losers had a higher proportion with diabetes.

Associations with fracture by baseline BMI, prior BMI change, and baseline WHtR in the full cohort

During at least 328,638 person-years of follow-up (median 8.7 years), 7290 individuals in the full cohort sustained a fracture of any type. Of these 4279 were fragility fractures including 1813 hip fractures. Age-adjusted HRs per SD of baseline BMI varied between 0.92 (95% CI, 0.90–0.95) for any fracture and 0.80 (95% CI, 0.75–0.84) for hip fracture; those for prior change in BMI between 0.96 (95% CI, 0.94–0.99) for any fracture and 0.80 (95% CI, 0.77–0.84) for hip fracture (Figure 2*A* and *C*). A lower rate of fracture with increasing baseline BMI was seen within every category of prior BMI change (Figure 2 *A-C*).

The inverse association between prior BMI change and fracture rate became less apparent with higher baseline BMI, a pattern that was seen for all fracture categories (p for heterogeneity ≤ .01). Specifically, higher prior BMI gain conferred lower rate of fragility and hip fracture within those with normal BMI, but not in those with obesity. Compared with those who gained BMI and were overweight, individuals with a normal baseline BMI who had prior loss in BMI had an HR of 1.23 (95% CI, 1.13–1.34) for any fracture, 1.53 (95% CI, 1.37–1.72) for fragility fracture, and 1.98 (95% CI, 1.64–2.38) for hip fracture. With use of the same reference group, gainers with a normal baseline weight had 28% to 45% higher fracture rates depending on type of fracture; although overall, gaining BMI in those with baseline obesity did not confer higher fracture rates. Results were robust after multivariable adjustment (Supplemental Fig. S2).

In contrast, central obesity as assessed by WHtR conferred higher rates of fracture in both women and men. The overall age- and BMI-adjusted HR per SD of WHtR was 1.12 (95% CI, 1.05–1.19) for hip fracture with no difference by sex (p = .26 for interaction), whereas modestly higher estimates were seen in men for any fracture (p = .037 for interaction) and fragility fractures (p for interaction .05). Both losers and gainer of BMI within the highest category of WHtR had higher rates of all types of fracture (Figure 3*A-C*), with the clearest associations for hip fracture.

Impact of baseline anthropometrics and body composition on the rates of fracture in the subcohort before and after adjustment for BMD

During a median follow-up of 10 years from baseline, 1088 women in the subcohort experienced an incident fracture of any type, 659 with a fragility fracture and 220 with a hip fracture. In accordance with results from the full cohort, one SD (4.3 kg/m^2) higher baseline BMI was associated with 8%, 12%, and 13% lower rate of any, fragility, and hip fractures, respectively (Table 2). Prior gain of BMI was also associated with lower fracture rate. There was

Table 1. Baseline characteristics of the participants in the full cohort (baseline 2009) and in the subcohort (baseline 2003–2009) by prior BMI change category

	Prior BMI change category					
	Full cohort (n = 44,366; 45.6% women)			Subcohort (n = 5022)		
Characteristic	BMI losers	BMI maintainers	BMI gainers	BMI losers	BMI maintainers	BMI gainers
Number of individuals, n (%)	11,817 (27)	22,277 (50)	10,272 (23)	540 (11)	1759 (35)	2613 (52)
Age (years), mean ± SD	72 ± 9	70 ± 8	68 ± 8	70 ± 8	68 ± 7	67 ± 6
BMI 1987–1990 (kg/m^2), mean ± SD	NA	NA	NA	24.7 ± 4.6	23.1 ± 3.1	23.7 ± 3.1
BMI 1997 (kg/m^2), mean ± SD	26.6 ± 3.8	24.9 ± 3.1	25.3 ± 3.6	NA	NA	NA
Baseline BMI 2008–2009 (kg/m^2), mean ± SD	24.5 ± 3.5	25.6 ± 3.1	29.0 ± 4.3	NA	NA	NA
Baseline BMI 2003–2009 (kg/m^2), mean ± SD	NA	NA	NA	22.8 ± 3.7	24.0 ± 3.2	27.9 ± 4.0
BMI change (kg/m^2), mean ± SD	−2.1 ± 1.6	0.7 ± 0.7	3.7 ± 2.3	−1.9 ± 2.5	0.9 ± 0.7	4.2 ± 2.0
Baseline waist-to-height ratio (cm/cm), mean ± SD	0.5 ± 0.1	0.5 ± 0.1	0.6 ± 0.1	NA	NA	NA
Baseline total lean mass index (kg/m^2), mean ± SD	NA	NA	NA	14.3 ± 1.3	14.4 ± 1.2	15.0 ± 1.4
Baseline appendicular lean mass index (kg/m^2), mean ± SD	NA	NA	NA	5.9 ± 0.7	6.0 ± 0.6	6.4 ± 0.7
Baseline total fat mass index (kg/m^2), mean ± SD	NA	NA	NA	7.4 ± 3.0	8.5 ± 2.6	11.6 ± 2.9
Baseline ratio of android to gynoid fat mass (kg/kg), mean ± SD	NA	NA	NA	0.4 ± 0.2	0.4 ± 0.1	0.5 ± 0.1
Baseline total hip BMD (g/cm^2), mean ± SD	NA	NA	NA	0.86 ± 0.13	0.89 ± 0.13	0.94 ± 0.13
Baseline height (cm), mean ± SD	171 ± 9.4	172 ± 9.1	170 ± 9.3	163.2 ± 6.4	163.8 ± 6.2	163.6 ± 6
No comorbidity at baseline, n (%)	7754 (66)	16,984 (76)	7367 (72)	434 (80)	1500 (85)	2272 (87)
Current smoker at baseline, n (%)	1069 (11)	1559 (8)	756 (9)	82 (15)	173 (10)	188 (7)
Daily alcohol intake before baseline (g), mean ± SD	6.3 ± 7.5	7.8 ± 8.1	7.2 ± 8.2	5.1 ± 6.3	6.2 ± 6.4	6.5 ± 7.7
Exercise in baseline year (h/week), n (%)						
<1	5562 (55.6)	10,293 (52.5)	5255 (58.8)	84 (16)	247 (14)	480 (18)
1	1208 (12.1)	2426 (12.4)	1058 (11.8)	86 (16)	294 (17)	490 (19)
2–3	1668 (16.7)	3566 (18.2)	1445 (16.2)	228 (42)	762 (43)	1096 (42)
4–5	1275 (12.7)	2770 (14.1)	995 (11.1)	65 (12)	224 (13)	318 (12)
>5	290 (2.9)	541 (2.8)	183 (2.0)	77 (14)	232 (13)	229 (9)
Diabetes mellitus at baseline, n (%)	1873 (16)	1610 (7)	991 (10)	52 (10)	89 (5)	101 (4)

Notes: Prior BMI change category: losers, BMI loss greater than 0.5 kg/m^2; maintainers, BMI loss lower than 0.5 kg/m^2 up to an increase by 2 kg/m^2; gainers, BMI increase by more than 2 kg/m^2. In the full cohort, prior change in BMI was estimated from self-reported change between 1997 and 2008–2009. In the subcohort, prior change in BMI was estimated from 1987–1990 to baseline. BMD measured by DXA.

Abbreviations: BMD, bone mineral density; BMI, body mass index; DXA, dual-energy x-ray absorptiometry; n, number of individuals; NA, not available; SD, standard deviation.

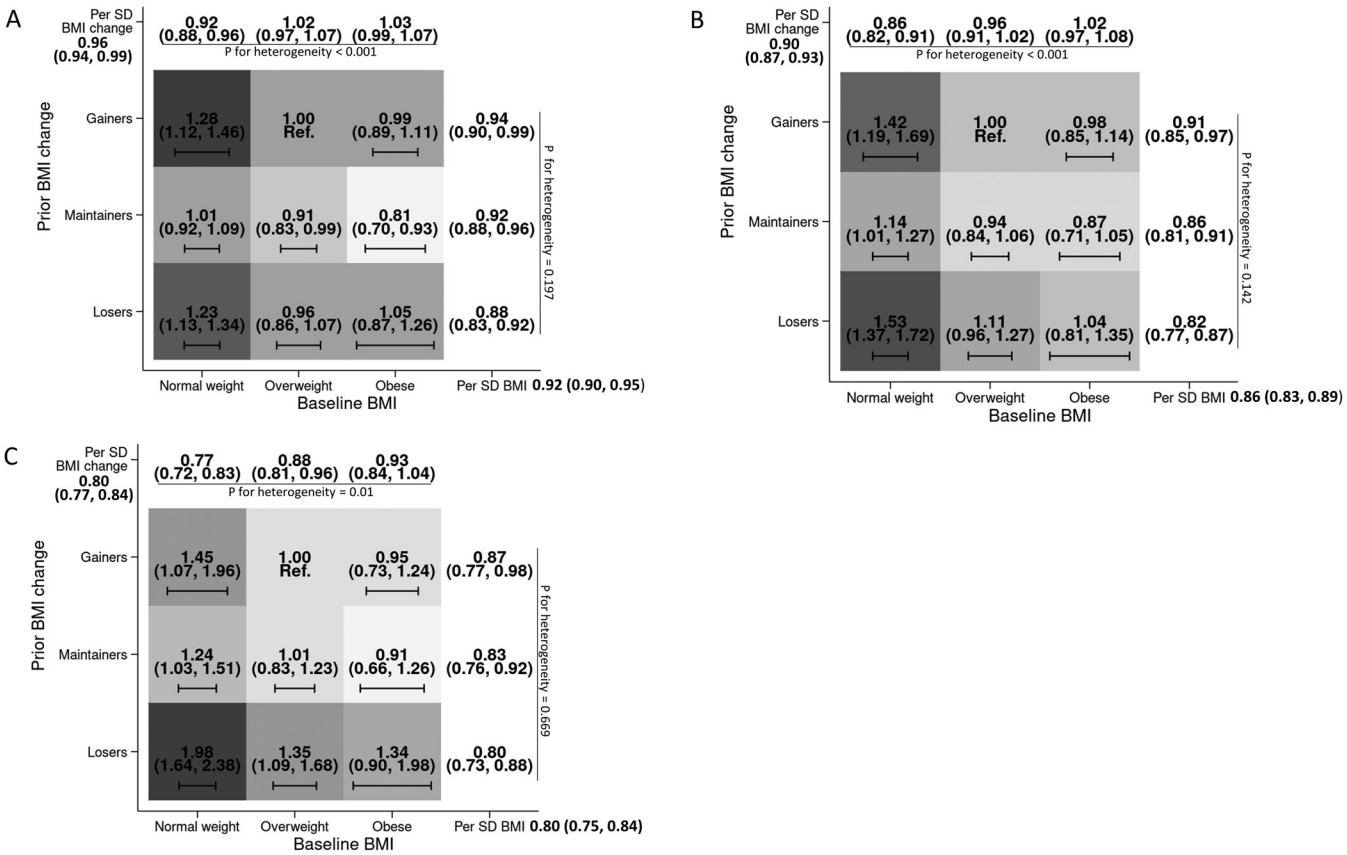

Fig. 2. Associations of combinations of baseline BMI in 2009 and prior change in BMI from 1997 to 2008–2009 with any fracture (*A*), fragility fracture (*B*), and hip fracture (*C*) in the full cohort. HRs were estimated by use of age-adjusted Cox regression analysis with overweight at baseline and prior gainers of BMI as the reference category. Within each cell, 95% CIs are presented below the HRs, both as numbers and as a line corresponding to the width of the CIs. Displayed in the margins of the heat map, within each stratum of prior change in BMI and baseline BMI, are age-adjusted HRs of fractures by per SD of BMI at baseline and per SD prior change of BMI. The overall HRs are shown below/behind the exposures. The *p* values for interaction between baseline BMI category and prior BMI change category are .068 (any fracture), .312 (fragility fracture), and .64 (hip fracture). Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; SD, standard deviation.

no statistically significant association between baseline total LMI and any fracture rate. In contrast, higher baseline appendicular LMI was associated with lower rate of fragility and hip fractures, with HRs of 0.92 per SD (95% CI, 0.85–0.99) and 0.89 per SD (95% CI, 0.78–1.02), respectively (Table 2). Similar estimates were obtained for baseline total FMI with HRs per SD of 0.88 (95% CI, 0.81–0.95) for fragility fracture and 0.87 (95% CI, 0.75–0.99) for hip fracture. After adjustment for BMD at baseline, BMI, total LMI, and total FMI conferred higher rates of fracture, especially hip fracture, with HRs/SD between 1.13 (total LMI) and 1.18 (BMI in 1987–1990) (Table 2). Appendicular LMI and prior BMI change were not associated with fracture rate in BMD-adjusted models. In comparison, each SD higher A/G FM was associated with 8% and 17% higher rate of any and hip fracture after adjustment for BMD. Body height was positively related to hip fracture rate before and after BMD adjustment.

Baseline android to gynoid fat mass ratio in relation to fractures within prior losers, maintainers, and gainers of BMI in the subcohort

In parallel with the analysis of WHtR in the full cohort, we examined the associations of baseline A/G FM with fractures within prior gainers, maintainers, and losers of BMI (Table 3). Higher central fat distribution; that is, central obesity, in BMI gainers conferred higher BMI- and BMD-adjusted fracture rates. The BMD-adjusted HR per each SD higher A/G FM ratio was 1.16 (95% CI, 1.05–1.28) for any fracture and 1.48 (95% CI, 1.16–1.89) for hip fracture. In contrast, the A/G FM was unrelated to hip fracture rate in BMI losers, with a BMD-adjusted HR of 0.99 (95% CI, 0.73–1.35) ($p = .046$ for heterogeneity across all prior BMI change groups).

Fracture rate in combination categories of *T*-score osteoporosis and low lean mass in the subcohort

Despite the overall association of appendicular LMI with fracture rate, low LM (appendicular LMI <5.45 kg/m^2) did not confer increased rate over that imposed by osteoporosis assessed by areal BMD (Supplemental Table S1). Compared with those with normal LM and no osteoporosis, the age-adjusted HRs for the combination of low LM and *T*-score osteoporosis were similar to those for *T*-score osteoporosis alone with, for example, HR of any fracture of 1.82 (95% CI, 1.41–2.36) and HR 1.80 (95% CI, 1.56–2.07), respectively. The corresponding HRs for hip fracture were 2.31 (95% CI, 1.40–3.80) and 2.50 (95% CI, 1.86–3.36). In

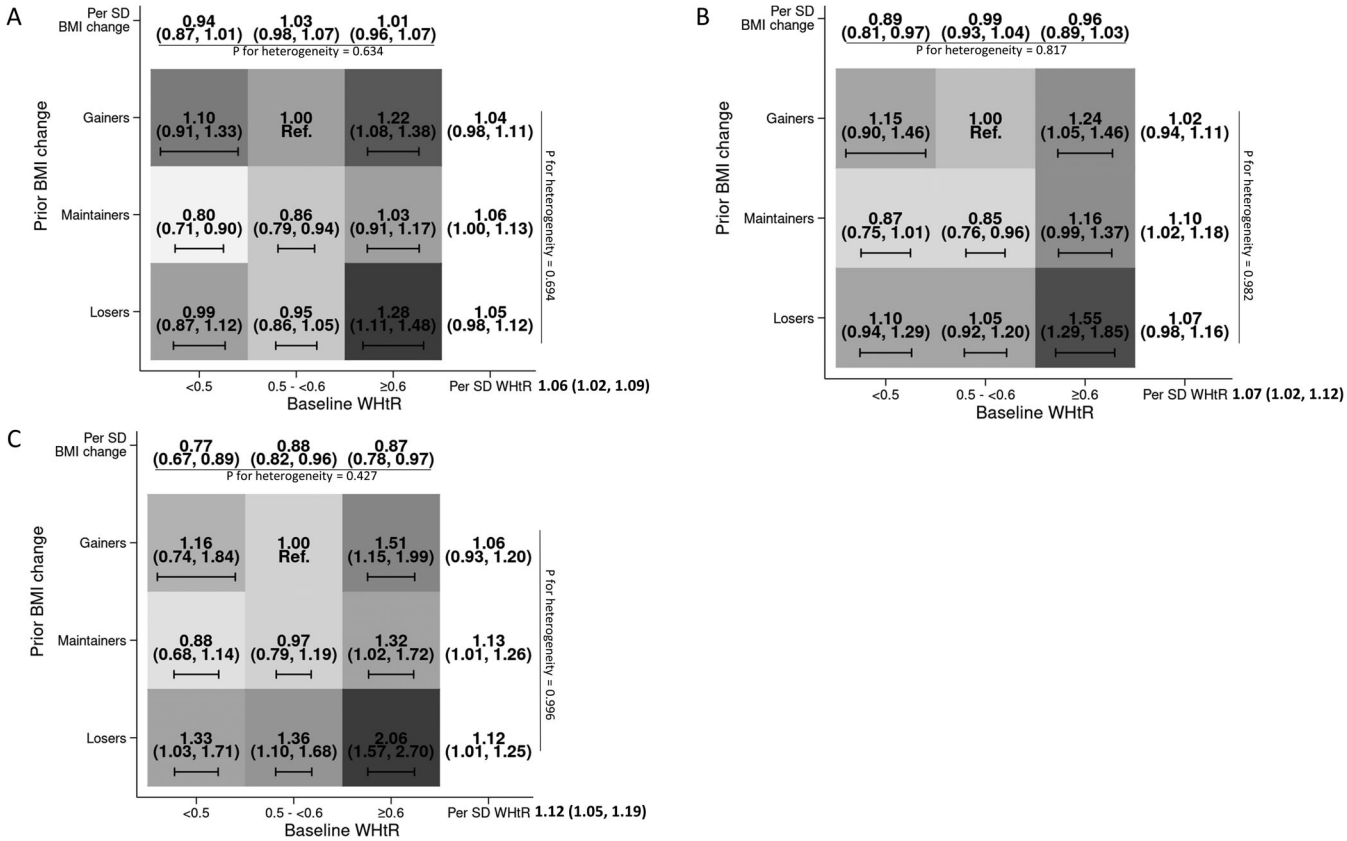

Fig. 3. Associations of combinations of baseline WHtR in 2009 and prior change in BMI from 1997 to 2008–2009 with any fracture (*A*), fragility fracture (*B*), and hip fracture (*C*) in the full cohort. HRs were estimated by use of age- and BMI-adjusted Cox regression analysis with WHtR values of 0.5 to <0.6 at baseline and prior gainers of BMI as the reference category. Within each cell, 95% CIs are presented below the HRs, both as numbers and as a line corresponding to the width of the CIs. Displayed in the margins of the heat map, within each stratum of prior change in BMI and baseline WHtR, are age-and BMI-adjusted HRs of fractures by per SD of WHtR at baseline and per SD prior change of BMI. The overall HRs are shown behind the exposure. The *p* values for interaction between baseline WHtR category and prior BMI change category are .231 (any fracture), .459 (fragility fracture), and .844 (hip fracture). Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; SD, standard deviation; WHtR, waist-to-height ratio.

addition, low LM without osteoporosis was not associated with fracture rate.

Sensitivity analysis

In sensitivity analyses, the underreporting of body weight had a negligible influence on the HR estimates for BMI in 1987–1990 and for prior BMI change (Supplemental Table S2). Mutual adjustment of the DXA lean and fat mass measurements only moderately changed the estimates of fracture rate (data not shown). Findings were similar in the multivariable-adjusted model (Supplemental Table S3) as well with further adjustment for previous fracture events or FRIDs use (data not shown) compared to the age-adjusted model.

Discussion

By use of two population-based cohorts we show that women and men with lower baseline BMI, prior loss in BMI, and higher central obesity display higher risk of fractures. These associations varied with the type of fracture; in general, the strongest associations were for hip fracture.

Baseline BMI, prior BMI change, and baseline WHtR and fracture risk

Beyond acquired BMI per se, the prior change of BMI is another risk factor for fractures which has been only sparsely investigated by others. In a prospective analysis of the Study of Osteoporotic Fractures, it is found that older women with 5% prior weight loss or more during a 6-year period have subsequent increased rates of hip-bone loss and twofold greater risk of subsequent hip fracture.[36] The authors find no statistically significant interaction between prior weight loss and baseline BMI or intention to lose weight. The analysis is based on measured weight and height, and 400 self-reported hip fracture cases during a 7-year follow-up of 6785 women.[36] The Tromsø study investigators, with use of time-dependent exposure analysis, find BMI loss to increase nonvertebral fracture risk in both nonsmoking women and men.[13] With a larger number of fractures, we were able to demonstrate that prior BMI gain had an overall protective effect on the risk of fracture. Conversely, the association of BMI with

Table 2. Adjusted HRs and 95% CIs of fractures by per SD higher value of anthropometric and body composition measures at baseline (2003–2009) of the subcohort (n = 5022)

Measure	Model 1, HR per SD (95% CI)[a]			Model 2, HR per SD (95% CI)[b]		
	Any fracture (n = 1088)	Fragility fracture (n = 659)	Hip fracture (n = 220)	Any fracture (n = 1088)	Fragility fracture (n = 659)	Hip fracture (n = 220)
BMI 1987–1990	0.94 (0.88–1.00)	0.92 (0.85–1.00)	0.97 (0.84–1.11)	1.05 (0.98–1.11)	1.05 (0.97–1.13)	1.18 (1.04–1.33)
Baseline BMI	0.92 (0.87–0.98)	0.88 (0.82–0.96)	0.87 (0.75–1.00)	1.07 (1.00–1.14)	1.06 (0.97–1.15)	1.16 (1.00–1.34)
Prior BMI change[c]	0.94 (0.89–1.00)	0.91 (0.85–0.98)	0.83 (0.73–0.94)	1.03 (0.96–1.10)	1.01 (0.93,1.10)	0.97 (0.83–1.12)
Baseline total LMI	0.98 (0.93–1.04)	0.96 (0.89–1.04)	0.99 (0.87–1.13)	1.07 (1.01–1.14)	1.06 (0.98–1.15)	1.13 (0.99–1.30)
Baseline appendicular LMI	0.96 (0.91–1.02)	0.92 (0.85–0.99)	0.89 (0.78–1.02)	1.05 (0.99–1.12)	1.02 (0.94–1.10)	1.03 (0.90–1.18)
Baseline total FMI	0.92 (0.86–0.98)	0.88 (0.81–0.95)	0.87 (0.75–0.99)	1.05 (0.99–1.12)	1.04 (0.95–1.13)	1.14 (0.98–1.32)
Baseline A/G FM	0.97 (0.91–1.03)	0.93 (0.86–1.00)	0.94 (0.82–1.09)	1.08 (1.02–1.15)	1.06 (0.97–1.15)	1.17 (1.02–1.35)
Baseline height	1.06 (1.00–1.13)	1.05 (0.97–1.14)	1.23 (1.07–1.42)	1.09 (1.02–1.16)	1.09 (1.00–1.18)	1.29 (1.12–1.48)

Abbreviations: A/G FM, the ratio of android (the abdominal area) to gynoid (the gluteofemoral area) fat mass; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; HR, hazard ratio; FMI, fat mass index; LMI, lean mass index; n, number of individuals; SD, standard deviation.

[a]Model 1: Baseline age-adjusted.

[b]Model 2: Model 1 with additional adjustment for BMD of total hip measured at baseline by DXA.

[c]Prior change in BMI was estimated from 1987–1990 to baseline.

fracture risk was observed in all three prior BMI change categories. Importantly, a higher WHtR (reflecting central obesity) in women and men conferred higher fracture risks after controlling for differences in BMI.

Baseline fat mass and fracture risk

For a more thorough understanding we need to further discuss the impact of body composition; that is, fat and lean mass in addition to BMD. In the subcohort of women, we observed that total FMI was associated with a reduced risk of fracture. A similar association of total body fat mass on classical fragility fracture risk (n = 85; including hip, spine, humerus, and forearm fractures) is suggested in the French Os des Femmes de Lyon (OFELY) study, also independent of BMD,[15] whereas the authors find no association with the BMD-adjusted risk for other types of major low-energy trauma fractures (n = 53).

Higher fat mass, and naturally also higher lean mass, contribute to increased BMD by mechanical loading.[7,37] Besides a weight-bearing effect, fat tissue could also positively affect the skeleton through sex hormonal regulation, adipokines and insulin-like growth factor-1 (IGF-1) metabolism, which all are important for bone health in men and postmenopausal women.[38–40] However, higher fat mass also leads to lower circulating 25-hydroxyvtamin D[41] and calcitriol, the active vitamin D metabolite.[42,43] Such an obesity effect can theoretically counter other consequences of a higher fat mass that protect against fractures. This is consistent with the tendency we observed of higher fracture risk with increasing BMI and FMI when BMD was taken into account in the subcohort.

In previous studies, worse physical performance is observed in overweight and obese elderly individuals,[44–47] a further explanation for our positive association between FMI and fracture risk after accounting for BMD. Poor muscle quality and function because of fat infiltration can be a feature of sarcopenic obesity.[47,48] Even though low BMD is a strong determinant of future risk of fragility fractures,[49] strategies to reduce fall rate and improve physical performance seem to be additionally effective for fracture prevention in the elderly.[50,51]

Our results based on the subcohort further deepen the understanding of mechanisms that lead to fractures because we showed the direct association of measured abdominal obesity with fracture risk after adjustment for BMI or BMD in women. When we focused our analysis in the full cohort on estimated central obesity by self-reported WHtR, higher ratios conferred higher rates of fracture in both women and men, which is consistent with A/G FM in the subcohort of women. Previous studies have shown that fat mass, but not central obesity, is positively related to plasma estradiol concentration[52] in postmenopausal women and testosterone level is negatively associated with central obesity in men.[53] Low levels of estradiol have been associated with low BMD and high risk of fracture in both men and women.[54,55] Beyond the possible mechanical cushioning effect of gynoid fat that can prevent hip fracture from occurring, aromatase activity, which is important for estradiol biosynthesis, is over 10 times more active in gluteal than in omental fat—an observation found in both sexes.[53,56]

It is noteworthy that fat distribution, as defined by the ratio of android to gynoid fat mass, has a closer association with cardiometabolic dysregulation than BMI.[57,58] Previous studies have indicated that higher android fat mass in both men and women is associated with higher risks of cardiovascular diseases, type 2

Table 3. Adjusted HRs and 95% CIs of fractures by per SD higher value of A/G FM within category of prior BMI change in the subcohort (n = 5022)

Prior BMI change category[a]	Any fracture (n = 1088) Adjusted HR per SD (95% CI)				Fragility fracture (n = 659) Adjusted HR per SD (95% CI)				Hip fracture (n = 220) Adjusted HR per SD (95% CI)			
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
Gainers (n = 2613)	1.06 (0.96–1.17)	1.14 (1.02–1.27)	1.16 (1.05–1.28)	1.19 (1.07–1.33)	1.03 (0.90–1.18)	1.14 (0.98–1.32)	1.15 (1.00–1.32)	1.20 (1.04–1.39)	1.24 (0.96–1.61)	1.34 (1.02–1.77)	1.48 (1.16–1.89)	1.46 (1.13–1.90)
Maintainers (n = 1759)	0.93 (0.84–1.02)	0.94 (0.84–1.06)	1.03 (0.93–1.14)	0.99 (0.88–1.12)	0.91 (0.80–1.03)	0.92 (0.79–1.06)	1.03 (0.90–1.17)	0.97 (0.84–1.13)	0.96 (0.77–1.19)	0.91 (0.71–1.18)	1.15 (0.92–1.43)	1.02 (0.79–1.31)
Losers (n = 540)	0.97 (0.83–1.12)	0.96 (0.80–1.15)	1.04 (0.89–1.21)	0.98 (0.81–1.17)	0.96 (0.79–1.16)	0.90 (0.71–1.14)	1.03 (0.84–1.26)	0.92 (0.73–1.17)	0.84 (0.62–1.14)	1.07 (0.74–1.54)	0.99 (0.73–1.35)	1.09 (0.76–1.57)

Notes: Follow-up of fractures was from baseline through 2017. Model 1: adjusted for age at baseline; Model 2: adjusted for age and BMI at baseline; Model 3: adjusted for age and total hip BMD at baseline; Model 4: adjusted for age, BMI and total hip BMD at baseline. BMD of total hip was measured by DXA.

Abbreviations: A/G FM, the ratio of android (the abdominal area) to gynoid (the gluteofemoral area) fat mass; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; DXA, dual-energy x-ray absorptiometry; HR, hazard ratio; n, number of individuals; SD, standard deviation.

[a]Prior BMI change category: losers, BMI loss greater than 0.5 kg/m^2; maintainers, BMI loss lower than 0.5 kg/m^2 up to an increase by 2 kg/m^2; gainers, BMI increase by more than 2 kg/m^2. Prior change in BMI was estimated in the time period from 1987–1990 to baseline.

diabetes, and impaired cognitive function,[59,60] diagnoses all additionally related to higher fracture risk.[61–63]

Baseline lean mass and fracture risk

Results from the French OFELY study suggest that increased total and appendicular LMI are associated with a lower risk of self-reported fractures in women and that adjustment for BMD only modestly attenuated the associations.[15] In the female subcohort, we also observed lower fracture risk with higher appendicular LMI, but total LMI failed to show an overall protective association against fractures despite its positive association with BMD (data not shown). In contrast, the BMD-independent impact of LMI, but not appendicular LMI, seemed to be associated with an increased fracture risk. The discrepancies in results for total LMI between the studies are difficult to explain given similar age and BMI distributions, but some possibilities might be differences in muscle performance related to low LMI and the methods used for fracture identification.

Our results may be an indication that muscle function is more important for fall and fracture prevention than lean muscle volume alone. In addition, "sarcopenia" as defined by the appendicular LMI cutoff[30] of <5.45 kg/m^2 was by itself unrelated to fracture risk and failed to provide additional prognostic value when combined with osteoporosis versus osteoporosis alone in our female population, in agreement with the Women's Health Initiative (WHI) study (n = 10,937).[64] These findings indicate that pharmacological interventions for treatment of sarcopenia may not reduce fracture risk and that a combination with exercise therapies to ameliorate physical function is needed.[65] Moreover, our findings also stress that low lean mass alone cannot fully capture muscle function and functional measures are to be preferred for the definition of sarcopenia.[66]

Strengths and limitations

Our study has several advantages. First, we used a large longitudinal population-based cohort including both women and men and a subcohort of women, both with prospective data collection from repeat questionnaires and long follow-ups. Second, we used an accurate method for fracture identification, including date and type of fracture, as well as mortality follow-up through complete national registries. The personal registration number provided to all Swedish citizens ensured no loss to follow-up. Third, we used a large number of anthropometric and body composition measures: our study was the first to include BMI, its changes and components including distributions and BMD in relation to fracture risk.

Our study was limited by having only a single DXA measured at our baseline of the subcohort and so we cannot at present investigate how changes in fat mass and lean mass associate with incident fractures. Self-reported BMI was used in the full cohort analysis, but according to our sensitivity analyses the underreporting had modest impact on our estimates. Discrepancies of self-reported compared to measured height and waist circumference were also modest and calculated changes in self-reported weight and height were similar to the measured changes. We were unable to distinguish between intentional and unintentional BMI loss.[36,67] However, we excluded individuals with prevalent cancer at baseline because cancer is a common cause of involuntary weight loss. There could be a possibility of selection bias up to the baseline in both the full cohort and the subcohort because those who lost BMI may have

been more vulnerable; for example, for an early death and thus not reaching the baseline. Nevertheless, this should not be a concern in causal inference research[68–70] if there exists sufficient exposure width and number of outcomes in each category of exposure. Finally, given a high number of comparisons some associations may have occurred by chance.

Conclusion

These findings demonstrate a complex pattern between anthropometrics/body composition and different types of fracture but display that for optimal fracture prevention, low BMI, prior BMI loss, and high central obesity should be avoided in both women and men.

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Disclosures

The authors declare no conflict of interest.

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Data availability statement

Data available upon application at https://www.simpler4health.se/.

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